# Studies of Cancer and Radiation Dose Among Atomic Bomb Survivors

## The Example of Breast Cancer

Charles E. Land, PhD

A comprehensive program of medical follow-up of survivors of the atomic bombings of Hiroshima and Nagasaki, Japan, by the Radiation Effects Research Foundation (RERF) has produced quantitative estimates of cancer risk from exposure to ionizing radiation. For breast cancer in women, in particular, the strength of the radiation dose response and the generally low level of population risk in the absence of radiation exposure have led to a clear description of excess risk and its variation by age at exposure and over time following exposure. Comparisons of RERF data with data from medically irradiated populations have yielded additional information on the influence of population and underlying breast cancer rates on radiation-related risk. Epidemiological investigations of breast cancer cases and matched controls among atomic bomb survivors have clarified the role of reproductive history as a modifier of the carcinogenic effects of radiation exposure. Finally, a pattern of radiation-related risk by attained age among the survivors exposed during childhood or adolescence suggests the possible existence of a radiation-susceptible subgroup. The hypothetical existence of such a group is lent plausibility by the results of recent family studies suggesting that heritable mutations in certain genes are associated with familial aggregations of breast cancer. The recent isolation and cloning of one such gene, *BRCA1,* makes it likely that the hypothesis can be tested using molecular assays of archival and other tissue obtained from atomic bomb survivor cases and controls.

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ALTHOUGH ionizing radiation is at most a minor contributor to the overall human cancer burden, the carcinogenic effects of radiation in human beings are probably better understood and almost certainly better quantified than those for any other common human carcinogen. Much of this information results from studies carried out by the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF).[1]

**See also pp 425 and 427.**

Beginning in 1947, the ABCC investigators initially focused on the genetic effects of exposure to ionizing radiation[2] and the abnormalities found by clinical and pathological examination of exposed persons.[1] The most significant event in the history of the research program was its reorganization during the middle to late 1950s as a unified, long-term epidemiological study of a fixed population, with emphasis on coordination of effort and integration of information from different substudies and research disciplines.[1] All studies were related to fixed subsets of a closed cohort of 285 000 survivors identified from a special supplement to the 1950 Japanese national census, plus a smaller number of nonexposed city residents located through other surveys at about the same time. The centerpiece of the program is the Life-Span Study (LSS), in which virtually complete mortality follow-up at the level of death certificate diagnosis was obtained on a probability sample, stratified by exposure distance, and confined to persons resident in the two cities on October 1, 1950. The LSS sample comprised 94000 atomic bomb survivors and 26000 nonexposed persons. Individual radiation doses have been estimated for more than 80% of the exposed sample members.[3,4] Ascertainment of cancer morbidity among LSS sample members was facilitated by the founding of tumor and tissue registries in collaboration with the local medical societies of Hiroshima and Nagasaki!

Asubsampleof15000 survivors, also selected on the basis of exposure distance, plus 5000 nonexposed sample members has been solicited since 1959 for participation in biennial clinical and laboratory medical examinations. Frozen serum samples and, more recently, immortalized lymphocyte cells have been stored for members of this subgroup.

Finally, a first-generation (Fl) sample of children conceived and born to survivors after the bombings was established to facilitate studies of possible genetic effects of radiation.

Over time, and especially in recent years, as those exposed during childhood or adolescence have reached ages at which cancer rates normally rise, cancer has emerged as the principal late health effect associated with radiation from the atomic bombs. Many organ sites are involved at various levels of effect. For several sites the number of cases and the ratio of excess to background cases permit investigation of questions that extend far beyond the existence and magnitude of a radiation effect. In this article, RERF investigations of breast cancer in women are presented to illustrate a typical RERF research path to evaluate radiation-related risk. This illustration includes cancer epidemiology, risk estimation, assessment of the interaction of radiation dose with other risk factors, assessment of genetic influences, and the potential for future investigations at the molecular level.

### BREAST CANCER INCIDENCE

Breast cancer risk among exposed women in the LSS sample is shown in Figure 1 as a function of radiation dose[6] In Figure 1, dose is used as an abbreviation for the weighted sum, gamma plus 10 times neutron dose to breast tissue, expressed in sieverts (Sv). Average yearly breast dose from natural background

From the Radiation Epidemiology Branch, National Cancer Institute, Bethesda, Md.

Reprint requests to Radiation Epidemiology Branch, National Cancer Institute, EPN 408, 6130 Executive Blvd, MS 7362, Bethesda, MD 20892-7362 (Dr Land)

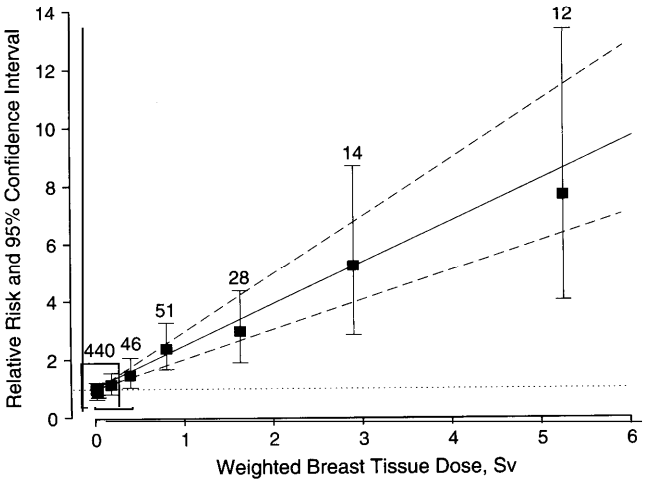


Figure 1.—Age-adjusted risk of incident breast cancer in women by radiation dose in sieverts (neutron weight=1O). Fitted relative risks (closed boxes) for intervals of radiation dose, plotted against the average dose for the subjects in the interval, and a fitted linear dose-response curve (solid line) are presented with average 95% confidence intervals (dashed lines) and error bars. Numbers of cancers in each dose interval are given above the error bar (adapted with permission from Tokunaga et a[6]).

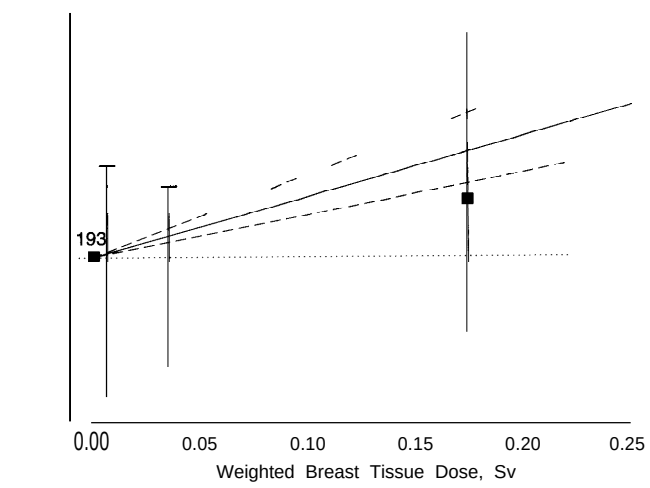


Figure 2.—Detail of Figure 1. Estimated relative risks (closed boxes) for weighted breast tissue doses below 0.25 Sv (O to 0.0009 Sv, 0.001 to 0.009 Sv, 0.01 to 0.09 Sv, and 0.10 to 0.249 Sv, respectively), with numbers of breast cancers displayed above the 95% confidence intervals (dashed lines) and error bars. The fitted linear dose-response curve (solid line) corresponds to all the points in Figure 1 and not just to those in Figure 2.

radiation in the United States is 1 mSv (0.1 rem), and the dose from a two-view film screen mammography with grid is about 2.3 mSv. Whole-body doses of more than 5 to 6 Sv are usually lethal.

Figure 1 represents 591 incident cases diagnosed from 1950 through 1985, among the 50946 female survivors with current radiation dose estimates. These women have been grouped into consecutive dose intervals. The data points represent the level of breast cancer incidence in each interval (plotted against average radiation dose) relative to the level of incidence in the lowest-dose interval. Of the 591 cases, 8790 were confirmed histologically.

Initial case ascertainment (ie, before review of available diagnostic materials and records) was carried out by the Tumor and Tissue Registry Office of the RERF, which searched the LSS Tumor Registry, the local tumor and tissue registries of Hiroshima and Nagasaki, the LSS death certificate series, and the RERF autopsy series for possible cases. The search also included the files of local hospitals and clinics known to treat breast cancer but whose contributions to the registries have been incomplete for one reason or another. Notification of deaths and ascertainment of death certificate diagnoses by the RERF are virtually complete for deaths occurring in Japan.[4] It is probably impossible to estimate the degree of cancer ascertainment by the LSS Tumor Registry since its founding in 1958, but by any measure of tumor registry efficiency that level is high. For example, only 2% of breast cancer diagnoses among that group were based solely on death certificates.[5] Various statistical methods can be used to adjust for incompleteness of ascertainment among the 20% of the sample who have migrated to other parts of Japan, including restricting inferences to locally diagnosed cases with appropriate adjustments to population denominators.[7] However, migration rates (and thus the proportion of cases missed because of migration) have not depended on radiation dose and therefore have virtually no effect on relative risk (RR) estimates like those presented in Figure 1.[8]

The registries support a comprehensive system of site-specific risk estimates in terms of cancer morbidity,[7] comparable in scope with the LSS mortality risk estimates based on death certificate diagnoses[4] that for years have been the principal basis for radiation-related risk estimates throughout the world. For cancers of low or long-delayed fatality, such as cancers of the breast, thyroid gland, salivary glands, and skin, morbidity data can be far more informative than mortality data. For example, 591 incident breast cancer cases represented in Figure 1 can be compared with 155 death certificates coded to breast cancer in women during the same period.[4]

### Variation of Risk by Radiation Dose

Figure 1 shows a radiation dose response corresponding closely to a linear model. Based on the estimated RRs at various doses, most of the 54 cancers among women with doses higher than 1 Sv (100 rem) are likely to have been caused by radiation, whereas few of those represented at the far left (440 among women with doses less than 0.25 Sv) were radiation related. The ability to compare cancers probably caused by radiation with other breast cancers in this series that probably were not caused by radiation is key to investigating characteristics of radiation-induced cancers and possible modifiers of radiation-related risk. The point is crucial: quantifying radiation risk is necessary, but our ambitions extend much farther. We want to understand the carcinogenic process, and we would also like to have more options for exercising control over risk. Options are especially needed for certain medical procedures (including the most effective treatment modalities for childhood cancer) in which complete avoidance of radiation exposure is not practicable.

Figure 2 is a detail of the lower left (low dose) corner of Figure 1. Of the 50946 exposed women with dose estimates in the LSS sample, 39894 or 7890 were assigned breast tissue dose estimates less than 0.1 Sv; another 1570 had doses less than 0.5 Sv, leaving only 7% with higher doses (Table). The data at very low doses are consistent with the linear dose-response curve fitted to the entire data set and plotted in Figure 2 ($P=.59$ for goodness of fit based on data from the O- to 0.25-SV interval).

In isolation, these data tell us hardly anything about risk; that is, they are of little value unless they are compared with higher-dose data. If we had only the data on survivors with doses less than 0.1 Sv, we would have no reason to conclude that radiation exposure increases breast cancer risk. In fact, as-

Estimated Number of Radiation-Related Breast Cancers Among Life-Span Study Sample, 1950 Through 1985, by Age at the Time of the Bombings (ATB) and Dose Interval*

| Age ATB, y | Estimated Radiation Dose to Breast Tissue, Sv | | | |
|---|---|---|---|---|
| | 0-0.1 | 0.1-0.5 | > 0.5 | Total |
| **0-19** | | | | |
| **No. of women** | **14702** | **2530** | **1370** | **18602** |
| **No. of cases** | **115** | **40** | **50** | 205 |
| Estimated No. (%) of radiation-related cancers | 3.6 (3.1) | 15.2 (38.0) | 36.2 (72.4) | 55.0 (26.8) |
| 20-39 | | | | |
| No. of women | 12964 | 2591 | 1225 | 18780 |
| No. of cases | 176 | 39 | 44 | 259 |
| Estimated No. (%) of radiation-related cancers | 2.6 (1.5) | 9.1 (23.3) | 26.8 (60.9) | 38.5 (14.9) |
| **> 40** | | | | |
| No. of women | 12228 | 2423 | 913 | 15564 |
| No. of cases | 94 | 22 | 11 | 127 |
| Estimated No. (%) of radiation-related cancers | 0.9 (1.0) | 2.3 (10.5) | 4.3 (39.1) | 7.5 (5.9) |
| **Total** | | | | |
| No. of women | 39894 | 7544 | 3508 | 50946 |
| No. of cases | 365 | **101** | **105** | **591** |
| Estimated No. (%) of radiation-related cancers | 7.1 (1.8) | 28.6 (26.3) | 67.3 (64.1) | 101.0 **(17.1)** |

*Consecutive dose intervals represented in Figures 1 and 2 have been combined for brevity. The number of radiation-related cancers was estimated by computing the probability of causation (PC) for each case and summing over all the cases in each group. As described in the text, PC = DxERR/(1+ DxERR$_{1Sv}$), where D is radiation dose in sieverts and ERR$_{1Sv}$ corresponds to the fitted function in Figure 3: ERR$_{1Sv}$=3.6 exp (–.0374 E), where E is age ATB in years.

suming that the fitted linear model estimated from the entire data set applies at low doses, even 400000 low-dose subjects, with a similar distribution of doses less than 0.1 Sv, would give less than a 70% chance of detecting the excess, and (more important) the confidence intervals for the risk coefficient would be very wide. Thus, an expanded study limited to low-dose survivors, involving eight times as many subjects as the current LSS sample and therefore costing about eight times as much, if it were done with comparable care and attention to detail, would be expected to yield comparatively little useful information. Indeed, much more care and attention to detail would be required to control for possible biases that could be safely ignored in a study with a substantial high-dose component.[9]

Even though most issues of regulatory concern involve low-dose and highly fractionated exposures, the disadvantages of basing risk estimates on studies of populations exposed only to low doses far outweigh the theoretical advantage of avoiding the problem of extrapolating risk estimates based on high doses to the low-dose region. The majority of atomic bomb survivors received low doses, but the strongest inferences about risk depend on contrasts between cancer rates at high and low doses. Moreover, the spectrum of high, medium, and low doses in the LSS population allows inferences to be made about the shape of the dose-response curve and also about the relationship between risks from high-dose and low-dose exposures. In the case of breast cancer, for example, the dose-response relationship does not deviate appreciably from linearity down to dose levels less than 0.5 Sv[6] and this relationship probably applies at lower levels as well. The influence of dose fractionation cannot be addressed with the atomic bomb survivor data alone, but comparisons with data from patient populations who received x-ray exposures in a few fractions and multiple fractions suggest that dose fractionation may not be an important modifier of risk.[10,11]

## Variation of Risk by Age at Exposure

The RERF study population includes substantial numbers of survivors at all exposure ages. Figure 3 shows the variation in the slope of the linear dose response as separately calculated for different exposure ages.[6] These estimates correspond to excess risk 12 or more years following the bombings or after the exposed women reached 30 years of age, whichever was later. Excess risk before this minimal latent period has not been observed.

The fitted curve in Figure 3 expresses the slope, or estimated excess RR at 1 Sv (ERR$_{1Sv}$), as a negative exponential function of exposure age. For any particular breast cancer case exposed at a given age to a given dose (D), the estimated likelihood that the cancer was caused by the exposure (PC or probability of causation) can be estimated as follows:

$$PC = DxERR_{1Sv}/(1+DxERR_{1Sv})$$

These estimates can be summed over the cases in any group. Thus, by 1985, about 55 of the 205 breast cancers observed among women who were not yet 20 years of age at the time of the bombings (ATB) would not have occurred in the absence of exposure. Among the 259 women between 20 and 40 years of age ATB and the 127 women 40 years of age or older ATB, about 38.5 and 7.5, respectively, would not have occurred in the absence of exposure (Table).

Breast cancer risk normally increases with increasing age at observation. Breast cancer is relatively rare before 35 years of age and extremely rare before 30 years of age. Since their number of excess breast cancers is already higher, the youngest survivors, who reached at least 40 and at most 60 years of age by 1985, have a greater lifetime per capita excess risk than women exposed during their 20s and 30s. A decline in risk during the next two decades cannot be ruled out, but there is little suggestion of that so far.

## Transfer of Risk Estimates Between Populations

One of the most uncertain aspects of risk estimation is how to apply to other populations risk coefficients derived from, and hence descriptive of, the atomic bomb survivor experience. For example, Japan has one of the lowest breast cancer rates in the world, whereas the United States has one of the highest, currently about four times as high as in Japan.[12] For ages 35 to 64 years, cumulative rates are 5.85% for the United States and 1.96% for the (mainly low-dose and nonexposed) contemporary residents of Hiroshima and Nagasaki. These cumulative rates can be used to represent the expected baseline risks for hypothetical US and Japanese women exposed to radiation at 25 years of age and observed between 10 and 40 years after exposure.

The estimated ERR for a female atomic bomb survivor who received a breast tissue dose of 0.1 Sv at 25 years of age is 0.14. The product of that ERR

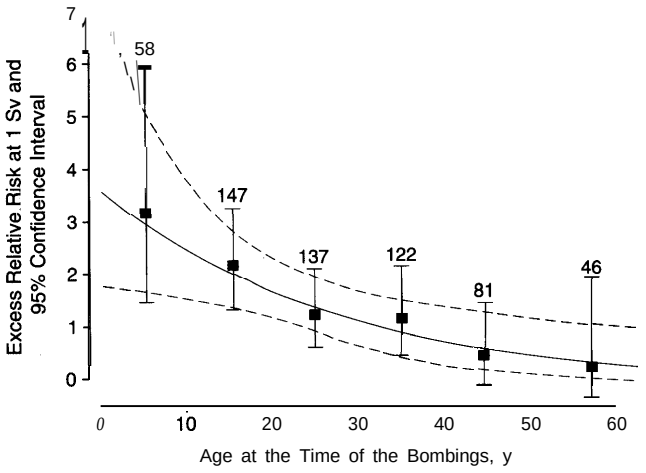


Figure 3.—Estimated excess relative risk (closed boxes) at 1 Sv ($ERR_{1Sv}$), with 957. confidence intervals (dashed lines) and error bars and numbers of cases, by interval of age at the time of the bombings. The fitted curve (solid line) with 95% confidence intervals represent $ERR_{1Sv}$ as a negative exponential function of exposure age (adapted with permission from Tokunaga et al[6]).

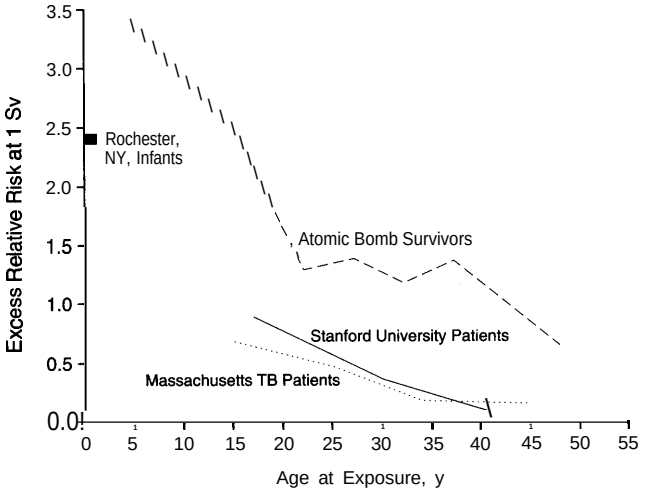


Figure 4.—Excess relative risk for the incidence of breast cancer in relation to age at exposure for atomic bomb survivors[8], Massachusetts tuberculosis (TB) patients given multiple chest fluoroscopes[13] and patients given x-ray therapy in Rochester, NY, for enlarged thymus in infancy[14] or at Stanford University for Hodgkin's disease[15] (adapted with permission from United Nations Scientific Committee on the Effects of Atomic Radiation").

and the baseline (ie, 0.14x1.96%=0.27%) is an estimate of the likelihood of a radiation-related breast cancer before 65 years of age, following exposure to 0.1 Sv at 25 years of age.

Because baseline breast cancer risks for a US population are different from those for a Japanese population, it cannot be true that both the ERR and the likelihood of a breast cancer associated with a given radiation exposure are the same for the two populations. Given estimates of both, derived from the atomic bomb survivor data, which (if either) should we use to characterize risk for a US population? That is, for a US woman exposed to 0.1 Sv at 25 years of age, should the likelihood of a radiation-related breast cancer before 65 years of age be estimated as 0.27%, the value estimated for an atomic bomb survivor, or as 0.82% (0.14 X5.85%), the product of the estimated ERR times the US baseline?

Fortunately, substantial data on breast cancer incidence in medically irradiated Western populations exist, enough for the appropriateness of the two transfer methods to be evaluated (Figure 4). In 1980, a parallel analysis of three exposed populations of women showed that exposure age–specific estimates of ERR at 1 Sv were markedly different between atomic bomb survivors and US women who received multiple chest fluoroscopes during treatment for tuberculosis or who were treated by x-ray for acute postpartum mastitis. However, excess rates among the three groups were comparable.[13] This finding may be confirmed by a wider-ranging and statistically more sophisticated analysis in progress, which compares breast cancer data from the LSS Tumor Registry[8] for the years 1958 through 1987 with other recent incidence data from several medically irradiated patient populations in the United States and Sweden.[14-17] However, risks among patients treated for benign breast disease may not fit the general pattern (Dale L. Preston, PhD, written communication, June 30, 1995). Thus, the preliminary results favor transfer of excess breast cancer rates between the LSS sample and irradiated US populations,[11] with the important caveat that other conditions, such as the existence of benign breast disease at the time of irradiation, may modify this relationship.

### Interaction of Radiation Dose With Other Breast Cancer Risk Factors

The higher breast cancer rates among US women and lower rates among women in Japan appear to be due to environmental and lifestyle factors rather than genetic differences between most Japanese and most Americans. Third and higher generations of US-born descendants of Japanese immigrants to the United States tend to experience breast cancer rates similar to those of other

scale, the factors responsible for the US-Japan difference do not appear to interact with radiation dose; the likelihood of a radiation-related cancer following a given exposure appears to be about the same in the two populations.

In all populations in which breast cancer has been studied, risk depends on reproductive history (eg, early age at first full-term pregnancy is associated with lower risk).[19] In an interview study of breast cancer cases and matched controls among atomic bomb survivors, the relationship between reproductive history and risk of breast cancer was found to be similar to that seen in other populations (Figure 5).[20]

However, the lack of synergism seen between radiation and the Japan-US difference in baseline rates did not hold for reproductive history and for radiation and age at first full-term pregnancy in particular. The following general interaction model expresses the RR of breast cancer given the age at first full-term pregnancy (A) and exposure to radiation dose (D):

$$RR(D,A)=(1+aD)(1+BA/[1+aD^{0}).$$

The model reduces to the additive model,

$$RR(D,A)=1+aD+BA,$$

for (0=1 and to the multiplicative model,

$$RR(D,A)=(1+aD)(1+BA),$$

when 0=0. The fitted value of the parameter O was –0.25 with 95% confidence intervals (–0.98 to 0.19), consistent with the multiplicative but not the additive model.[21] That is, both baseline rates and radiation-related excess rates were reduced for women with early full-term pregnancies and in about the same proportions (ie, the two factors appeared to be synergistic on an additive scale).

Even more interesting, the dependence between radiation-related risk and age at first full-term pregnancy held whether exposure preceded or followed

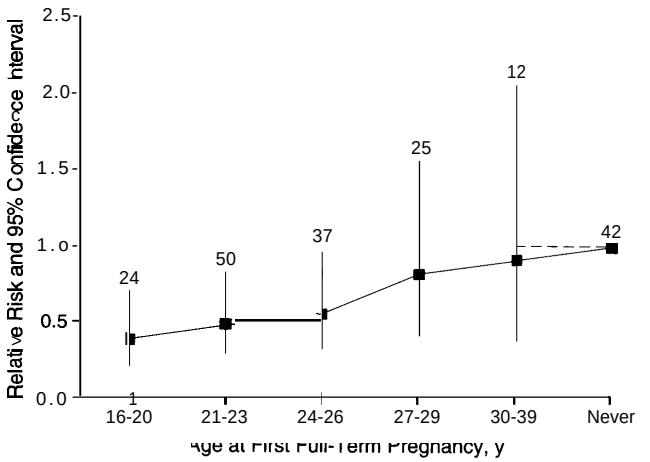


Figure 5.—Relative risk (closed boxes) of breast cancer by age at first full-term pregnancy among atomic bomb survivors. Numbers of cases are given above the error bars for each data point (adapted with permission from Land et a1[20]).

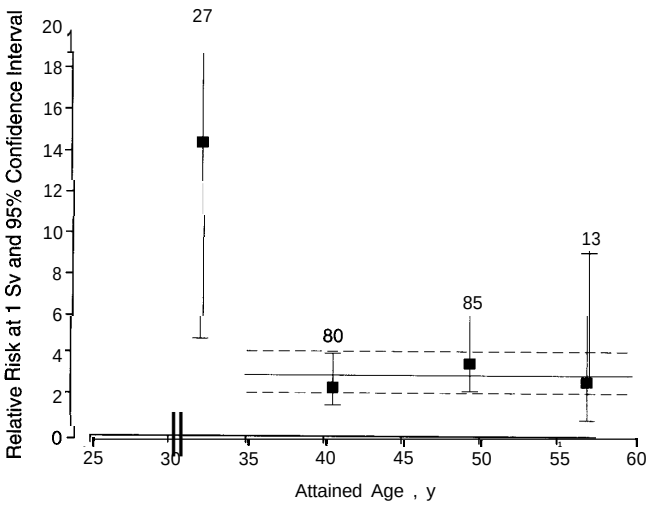


Figure 6.—Estimated excess relative risk (closed boxes) at 1 Sv for breast cancer among female atomic bomb survivors exposed before 20 years of age, for attained ages 25 through 34 years, 35 through 44 years, 45 through 54 years, and 55 through 60 years, with 95% confidence intervals, error bars, and numbers of cases. Horizontal lines correspond to the pooled estimate (solid line) and confidence intervals (dashed lines) for attained ages 35 through 60 years (reprinted with permission from Land et a1[20]).

the first pregnancy. Excess risk among women exposed as young girls (at age 16 years or younger) was reduced by a subsequent full-term pregnancy at a young age and increased by nulliparity or a late first pregnancy. The finding suggests that terminal differentiation of cells for milk secretion, induced by a full-term pregnancy, may reduce the proliferative potential even of cells already initiated by radiation.

This interpretation is consistent with experimental results obtained by Clifton et al.[22,23] In their study, female rats were irradiated and injected with prolactin-secreting, transplantable pituitary tumors. One group received no further treatment; another received adrenalectomy, which precluded the production of adrenal corticoids necessary for cell differentiation for milk secretion, and a third group received both adrenalectomy and glucocortisol replacement therapy. High levels of radiation-induced mammary cancer were experienced by the adrenalectomy-only group compared with rats with intact adrenals oradrenalectomized rats given glucocortisol replacement therapy.

## POSSIBLE GENETIC INFLUENCES ON SUSCEPTIBILITY TO RADIATION CARCINOGENESIS

The final breast cancer example is a work in progress. It began with the question of whether the high radiation-related RRs among women exposed at young ages are likely to continue. Figure 6 shows $ERR_{1Sv}$ among women exposed during childhood or adolescence, ie, before 20 years of age, separately estimated by age at diagnosis.[6,24]

Figure 6 is dominated visually by $ERR_{1Sv}$= 13.5 (RR=14 .5) for diagnosis before 35 years of age, compared with $ERR_{1sv}$=2.0 for later diagnosis. Could there be a genetic basis for this remarkable and statistically significant difference? In the United States, a high percentage of early-onset breast cancer cases are thought to be familial, many associated with inherited mutations in the *BRCA1* and *BRCA2* genes that are also thought to be involved in 5% to 10% of US breast cancers.25 Early-onset breast cancer is also associated with the rare Li-Fraumeni syndrome, which involves heritable mutations in the p53 tumor-suppressor gene.[26] Ataxia-telangiectasia heterozygotes may be at increased risk of breast cancer, and it has been suggested (but not demonstrated) that these individuals may have increased sensitivity to radiation carcinogenesis,[27] as has been shown for soft-tissue sarcoma and osteosarcoma in patients with hereditary retinoblastoma.[28]

The high risk of radiation-related, early-onset breast cancer illustrated in Figure 6 has not been observed in any other series. The lack of similar observations may be the result of the other series not having such a large number of radiation-related breast cancers among women exposed during childhood and adolescence or the low level of baseline risk found in Japan and possibly because the phenomenon might be a chance occurrence. Nevertheless, this anomaly should be explored. One possibility is that there is a radiation-sensitive genetic subgroup in the LSS population. Family pedigrees are currently being constructed at the RERF using the LSS and F1 study samples. Numbers of relevant cancers among family members are being determined through tumor registry matches. Currently, we do not know the extent to which heritable mutations may play a role in breast cancer risk in the general Japanese population or in the higher-risk but genetically similar population of third- and later-generation Japanese Americans.

With the rather surprising exception of the early-onset spike shown in Figure 6, ERRs for breast cancer, once established, tend to be fairly stable over time following exposure at any given age.[6] This pattern is in sharp contrast to leukemia risk following childhood exposure, which is thought to increase sharply about 2 years after exposure followed by a more gradual decline to zero.[29] Thus, for breast cancer, factors related to attained age but unrelated to radiation appear to determine when and probably whether both radiation-related and background breast cancers will occur. In kindreds at increased risk of breast cancer because of heritable mutations, breast cancers tend to be diagnosed at earlier ages than in the general population, but not all mutation-related cancers are diagnosed at young ages.[30] Thus, even for a powerful risk factor present from conception, the expression of risk awaits developmental events; the timing and perhaps even the likelihood of occurrence appear to depend at least partially on events unrelated to the mutation.

If the high radiation-related RR observed for early-onset breast cancer among the LSS sample is indeed a function of genetic susceptibility, an interesting question is whether the observation simply reflects the uneven mix of heritable mutation involvement in breast cancers diagnosed at different ages. The magnitude of risk might be differentially affected by radiation for two genetic groups, whereas within groups, the timing of risk might be unaffected. Thus, the RRs could be high before 35 years of age because disproportionately many of the breast cancers diagnosed in the general population at those ages occur among women with an inherited predisposition to breast cancer and because such women also are highly sensitive to radiation carcinogenesis. An alternative hypothesis is that radiation exposure may, in the presence of an inherited predisposition, take the place of one or more of a series of age-related events needed for the appearance of a cancer and thus bring forward in time a cancer that already had a high likelihood of occurrence.

## THE POTENTIAL FOR INVESTIGATIONS AT THE MOLECULAR LEVEL

With the exception of hereditary retinoblastoma patients treated by radiation, who tend to develop soft-tissue sarcomas or osteosarcomas in the radiation field,[%] there is little information for any human population on how genetic predisposition may modify the carcinogenic effects of ionizing radiation exposure. The recent sequencing of the *BRCA1* breast cancer susceptibility gene[31] and assays for mutations in that gene among members of families at high risk of breast cancer,[32] the identification of *BRCA2* and indications of the possible existence of yet another susceptibility gene,[30] as well as the recent cloning of the *ATM* gene thought to be responsible for ataxia telangiectasia,[33] suggest that someday we may determine by molecular assay whether selected cases and controls have heritable mutations. We may also be able to evaluate the frequency of such mutations in different population subgroups.

The retrieval of such information for the LSS populationis likely to be a daunting task in terms of both technology and organization. Once obtained, it may be possible to model genetic susceptibility to radiation carcinogenesis as an interaction problem. That is, are the two factors additive, in that the dose-dependent likelihood of a radiation-related breast cancer (absolute risk) is independent of the presence or absence of particular heritable gene mutations; multiplicative, in that the dose-dependent ERR is independent of heritable mutations; or does the association differ from both of these two simple patterns?

Materials potentially available for molecular assay include stored lymphocytes that, during recent years, have been cryopreserved for some 5000 participants in the RERF's clinical program, although relatively few of the women who previously or subsequently developed breast cancer are included. For most breast cancer cases, tumor tissue and adjacent normal tissue, obtained by surgery, biopsy, or autopsy, are stored at various medical institutions in the form of slides and formalin-fixed paraffin blocks. There is also the possibility of soliciting blood samples from living members of the LSS population not included in the clinical subsample.

## CONCLUSION

One of the ultimate goals in risk protection is to identify those at greatest risk from exposure. An important purpose of studying cancer in irradiated populations is to understand, control, and modify the carcinogenic process. These goals now seem more attainable than they once did. The recent advances in molecular biology, our increasing understanding of the genetic basis of cancer, and the fact that we know more about radiation as a cause of cancer than any other environmental human carcinogen have created many opportunities for future research.

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